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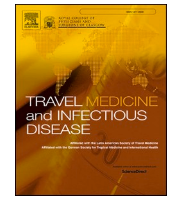

Review

COVID-19 sequelae in adults aged less than 50 years: A systematic review

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ABSTRACT

Background: There is emerging evidence of long-term sequelae in a considerable proportion of COVID-19 patients after recovery and the spectrum and severity of such sequelae should be systematically reviewed. This review aims to evaluate the available evidence of all intermediate and long-term COVID-19 sequelae affecting formerly healthy adults.

Methods: A systematic literature search of Embase, WHO, Scopus, Pubmed, Litcovid, bioRxiv and medRxiv was conducted with a cutoff date of the 17th September 2020 according to PRISMA guidelines and registered in PROSPERO (CRD42020208725). Search terms included "COVID-19", "coronavirus disease 2019", "SARS-CoV-2", "sequelae" and "consequence*". Publications on adult participants, with a confirmed SARS-CoV-2 infection were included. Elderly (>50 years old) and children (<18 years old) were excluded. Bias assessment was performed using a modified Newcastle-Ottawa Scale.

Results: A total of 31 papers were included. Study types included prospective and retrospective cohort studies, cross-sectional studies and case reports. Sequelae persistence since infection spanned 14 days to three months. Sequelae included persistent fatigue (39–73% of assessed persons), breathlessness (39–74%), decrease in quality of life (44–69%), impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39–83%), evidence of peri-/perimyo-/myocarditis (3–26%), changes in microstructural and functional brain integrity with persistent neurological symptoms (55%), increased incidence of psychiatric diagnoses (5.8% versus 2.5–3.4% in controls), incomplete recovery of olfactory and gustatory dysfunction (33–36% of evaluated persons).

Conclusions: A variety of organ systems are affected by COVID-19 in the intermediate and longer-term after recovery. Main sequelae include post-infectious fatigue, persistent reduced lung function and carditis. Careful follow-up post COVID 19 is indicated to assess and mitigate possible organ damage and preserve life quality.

1. Introduction

Although SARS-CoV-2 predominantly affects the respiratory system, several studies and interim reports indicate that COVID-19 is a multisystem infection with both overt and subtle health consequences. Data on how long symptoms persist, the impact of such symptoms on everyday life and the short-term, intermediate and long-term sequelae of this infection have scarcely been researched. Most original data publications focus on patients who have been hospitalized, on individuals who have suffered severe illness or on older patients with comorbidities. There are few studies following up on young people who have tested SARS-CoV-2 positive and who have experienced mild illness or indeed, been asymptomatic while testing positive. Such data are particularly important in terms of projecting the future burden of COVID-19 sequelae on healthcare systems and also in the context of "fitness to work" of young population groups as young adults constitute a large proportion of any country's workforce.

In the ongoing pandemic, evidence is emerging of individuals suffering from debilitating symptoms weeks and even months after COVID-19 diagnosis. This is of great concern to the medical community. The large number of such cases becomes apparent when looking at the size of groups such as the so called "*COVID long haulers*" on social media,

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the members of such groups often number thousands [1]. Several small studies have followed up on recovered COVID-19 cases, particularly on severe cases. However, a systematic and evidence-based review on long-term COVID-19 sequelae in previously healthy adults is missing.

In this systematic review, we identified and summarized original data published until mid-September 2020. The focus was on formerly healthy young to middle-aged adults. Children and elderly were excluded. Speculations on possible consequences, that may be anticipated in the future based on experiences from other viral infections, complemented this review in the discussion section.

2. Material and methods

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42020208725.

2.1. Data sources and searches

A systematic search of published papers and preprints was performed in the databases Embase, PubMed, Scopus, WHO, LitCovid, bioRxiv and medRxiv. The search terms were selected to find papers on sequelae to a SARS-CoV-2 infection and included the terms “COVID-19”, “coronavirus disease 2019”, “SARS-CoV-2”, “sequelae” and “consequence*”. The terms “child*” and “pregnant” served as negative qualifier. The online searches were performed between 15th and 17th September 2020. The complete search strategies are included in the Supplement (Appendix 1).

2.2. Data management

References found through the systematic search were imported into Mendeley, a reference management tool. After a first elimination of duplicates, a single reference file was generated and uploaded into the Covidence online tool, a non-profit service for screening and facilitating the systematic review process [2]. The assessment of inclusion or exclusion of every reference was performed by two out of eight independent reviewers (N.B., N.H., A.H., R.L., C.S., D.S., K.S., S.W.) according to predefined criteria. Only studies including original data and systematic or narrative reviews published up to 15th September 2020 were included. Only English language papers were included. References including children (below the age of 18 years) or only elderly (age 50 years and above) were excluded. The goal of this systematic review was to focus on young adults aged 18–50 years as they make up the majority of the working population. COVID-19 in this group was initially considered to be a mild illness. In the interim, evidence is emerging of persistent sequelae even in previously healthy young populations. Other systematic reviews have looked at COVID-19 sequelae in the elderly, the polymorbid or those who were hospitalized with severe illness. In such groups, it is more difficult to distinguish sequelae of COVID-19 from other disease progression. Children were excluded due their differing anatomy and physiology and their seemingly lower susceptibility to SARS-CoV-2 virus which makes it difficult to compare them to adults directly. Additionally, study subjects had to have a confirmed SARS-CoV-2 infection. Both sexes and formerly healthy participants as well as participants at risk (as defined by WHO [3]) were included. The study period had to include the follow-up after usual recovery and/or discharge from hospital. Animal, laboratory or in vitro studies were excluded. Any discrepancies were resolved by a third reviewer. The full text screening was performed by two independent reviewers (either K.S. and S. W. or N.B. and S. W.). Conflicts in the full text screening were resolved by discussion. The included studies were carefully screened for other references containing original data that fit the inclusion criteria and were missed by the systematic search.

All the studies finally included were summarized in tables according to organ system. A bias assessment of all cohort and cross-sectional studies was performed by two independent reviewers (R.L. and S.W.) using a modified version of the Newcastle-Ottawa Scale (mNOS) for assessing the quality of non-randomized studies [4] as presented in the Supplement. Discrepancies were resolved by discussion. In addition, an analysis of the evidence level according to the JAMA network (modified from Oxford Centre for Evidence-based Medicine) was carried out for each study [5].

3. Results

A total of 5229 references were retrieved during the search and imported into Mendeley where 2478 duplicates were removed. Covidence recognized another 30 duplicates, leaving 2721 references for title and abstract screening. A total of 2540 references were deemed irrelevant during the title and abstract screening. Of the remaining 181 references, 18 references containing original data were finally included during the full text review. Additionally, there were 13 studies identified through screening of the included references and through other sources. Fig. 1 shows the PRISMA flow chart diagram [6]. Included studies comprised of 11 prospective and 11 retrospective cohort studies, 4 cross-sectional studies and 5 case reports.

All the references included in this review were summarized in Table 1 including the study quality ratings from the modified Newcastle-Ottawa Scale. Scores were classified as unsatisfactory (0–3 points), satisfactory (4–5 points), good (6–7 points) and very good (8–9 points). A total of four studies were awarded “very good”, while five studies received a “good” rating. A majority of 12 studies were deemed “satisfactory”. Five studies only received three points and therefore were rated as “unsatisfactory”. As the modified Newcastle-Ottawa Scale is not suitable for rating case reports, the remaining five case reports were only rated according to the evidence level as defined by the JAMA network [5]. The detailed rating of each study can be found in eTable 1 in the Supplement.

Only information and subpopulations relevant for this review were listed.

3.1. General health

Two prospective and two retrospective cohort studies as well as three cross-sectional studies were grouped under the term “general health” [7–13].

The follow-up intervals lasted between 14 days and 12 weeks. Five out of these six studies reported persistent fatigue in 39–72% of study participants [7,9–12]. Breathlessness or shortness of breath was reported by four out of six, ranging from 39 to 74% [7,8,10,11]. In five studies, a reduction in life quality or general health status was observed [7,8,10–12]. In one study, 31% of formerly employed participants have not returned to work at approximatively 72 days post-discharge [9]. Another study reported functional restrictions (e.g. changes in life-style, sports and social activities) in 80% of participants, albeit 63% thereof was considered negligible [13].

3.2. Respiratory system

There were two prospective and eight retrospective cohort studies and one case report containing information regarding the respiratory system [14–24].

Eight out of 11 studies used computed tomography [16–19,21–24]. Six out of 11 performed a lung function test [14–16,20,23,24]. Follow-up intervals ranged from nine days to three months post-discharge from hospital. Abnormal CT findings were found in 39–83% of study participants. Five studies described pulmonary fibrosis as a radiological finding [17,18,20,22,24], while hypoperfused lung volume was found in one study [19]. Impaired lung function was observed in 19–75% of the study population [14–16,20,23,24].

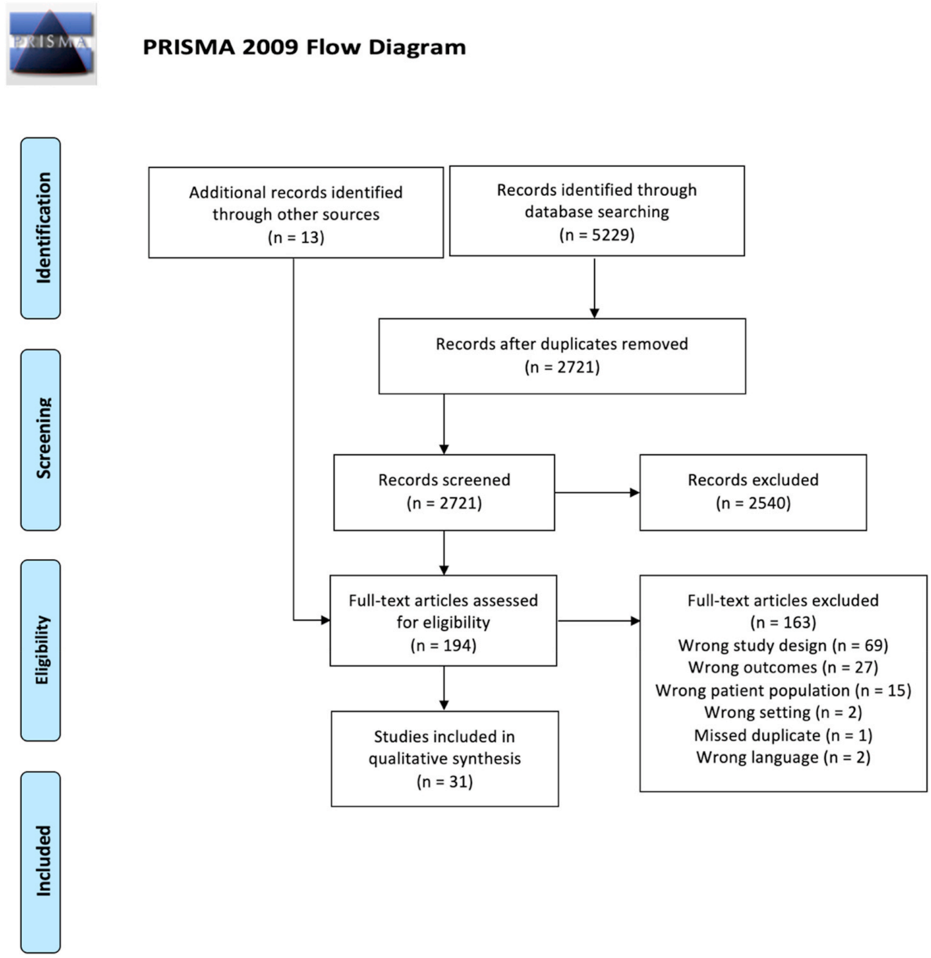

Fig. 1. PRISMA flow diagram.

3.3. Cardiovascular and hematological system

References classified into the cardiovascular and hematological category included two prospective cohort studies, one cross-sectional study and one case report [25–28].

Time to follow-up examination varied from 11 days after quarantine to approximately three months post-diagnosis. Three studies performed cardiac magnetic resonance imaging and observed evidence of peri-, myoperi- and myocarditis in 3–26% of the participants [25–27]. One study showed altered immune cell counts 9–11 weeks after symptom onset [25], while a case report described isolated thrombocytopenia in a patient approximatively one month after symptom onset [28].

3.4. Neurological system and mental health

Two studies, a prospective cohort study and a case report, described neurological complications [29,30] while one prospective and one retrospective cohort study investigated psychiatric sequelae [31,32]. In one study, a MRI follow-up after three months showed disruptions to microstructural and functional brain integrity and 55% of participants complained about persistent neurological symptoms [29]. A case report showed persisting lower limb weakness one month after symptom onset [30]. An increased incidence of 5.8% of newly diagnosed psychiatric diseases 14–90 days after diagnosis of COVID-19 infection was shown in a large cohort study in comparison to a control group where 2.5–3.4% of participants received a new psychiatric diagnosis [31]. The other reference described a prevalence of at least one psychopathological dimension approximately one month post-discharge or after evaluation at the emergency department in 56% of study participants [32].

3.5. Otorhinolaryngological system

A total of three prospective cohort studies examined olfactory and gustatory dysfunction after COVID-19 [33–35]. The follow-up intervals ranged from 12 to 39 days after symptom onset. There was a lack of recovery of gustatory and/or olfactory function in 3–13.9% of study participants. Incomplete recovery was observed in 33.6–36% of participants at follow-up.

3.6. Endocrinological system

There were two case reports describing subacute thyroiditis (SAT) 15 days and six weeks after symptom onset, respectively [36,37]. In both cases there was a clinical and laboratory resolution of SAT within two weeks of adequate therapy.

4. Discussion

There is an ever-expanding body of knowledge regarding the acute effects of a SARS-CoV-2 infection on several organs. So far, it is known that SARS-CoV-2 can infect lung, heart, liver and kidney tissue, gastrointestinal mucosa, vascular endothelium, macrophages, T-lymphocytes and neurons [38]. In addition to the direct damage through the viral infection, in some patients the infection leads to a massive release of cytokines, a cytokine storm, which indirectly results in extensive tissue damage [39]. As a consequence, in every affected organ, directly or

Table 1
Summary of references reporting long-term sequelae of COVID-19.

Author, Year	Title	Journal	Study type	Participants	Eligibility criteria	Follow-up time	Examination methods	Main outcomes	mNOS rating	Evidence level
General Health										
Halpin et al., 2020 [7]	Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation	Journal of Medical Virology	Cross-sectional study	68 ward patients (20-93y, 48.5% female) and 32 ICU patients (34-84y, 40.6% female)	Treated for COVID-19 within Leeds Teaching Hospitals NHS Trust; RT-PCR confirmed	29–71 days post-discharge (mean 48d)	Telephone screening tool	Illness-related fatigue (72% ICU group, 60.3% ward group); breathlessness (65.6% in ICU group, 42.6% ward group); psychological distress (46.9% ICU, 23.5% ward group); drop in the EQ-5D instrument (68.8% ICU and 45.6% ward group)	5	4
Weerahandi et al., 2020 [8]	Post-discharge health status and symptoms in patients with severe COVID19	Preprint	Prospective cohort study	152 patients (IQR 50-67y, 37% female)	>18y old; required at least 6l O2 during hospital stay; RT-PCR confirmed	30–43 days post-discharge (median 37d)	Survey instrument (PROMIS)	Shortness of breath 74.3%; drop of 1 out of 5 points in PROMIS Global Health-10 instrument	5	3[a]
Townsend et al., 2020 [9]	Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection	Preprint	Cross-sectional study	128 (mean 49.5± 15y, 54% female)	At least 6 weeks after date of last acute symptom (outpatient) or date of discharge; RT-PCR confirmed	72 days (IQR 62-87d) post-discharge or post-diagnosis + 14d	Chalder Fatigue Score	Persistent fatigue 52.3%; formerly employed not returned to work 31%	6	4[a]
Arnold et al., 2020 [10]	Patient outcomes after hospitalization with COVID-19 and implications for follow-up; results from a prospective UK cohort.	Preprint	Prospective cohort study	110 (ICR 46-73y)	>18y old; RT-PCR confirmed or clinic-radiological diagnosis	8–12 weeks after admission	Chest radiograph (HRCT), spirometry, exercise test, blood test, HRQoL questionnaire	At least one persistent symptom 74%; including breathlessness (39%), excessive fatigue (39%) and insomnia (24%); 2 with fibrotic changes in HRCT; 11 with restrictive pattern spirometry; 15 with desaturation in sit-to-stand test; reduced SF-36 health status	5	3[a]
Carfi et al., 2020 [11]	Persistent Symptoms in Patients After Acute COVID-19	JAMA	Retrospective cohort study	143 (19-84y, 37% female)	Diagnosis of COVID-19; negative test at study begin	Mean of 60 days (SD 13.6d) after symptom onset	Comprehensive medical assessment, standardizes questionnaire	Persistent symptoms 87.4% (fatigue 53.1%, dyspnea 43.3%, joint pain 27.3%, chest pain 21.7%); Worsened quality of life 44.1%	6	3
Tenforde et al., 2020 [12]	Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020	Morbidity and Mortality Weekly Report	Retrospective cohort study	292 respondents, 274 symptomatic (IQR 31-54y, 52% female)	>18y old; RT-PCR confirmed	14–21 days (median 16d) after test date	Telephone interviews	One or more symptoms 94% (fatigue 71%, cough 61%, headache 61%); among symptomatic responders not returned to usual state of health 35% (26% among those aged 18-34y, 32% among those aged 35-49y)	4	3
Mohamed Hussein et al., 2020 [13]	Post-COVID-19 Functional Status: Relation to age, smoking, hospitalization and comorbidities	Preprint	Cross-sectional study	444 (18-86y, 252/444 female)	RT-PCR confirmed or presumed on clinical & radiological criteria	35.31±18.75 days since onset of symptoms	Online forms, Post-COVID-19 functional status scale	80% of recovered with diverse degrees of functional restrictions (63.1% negligible, 14.4% slight, 2% moderate, 0.5% severe)	4	4[a]
Respiratory System										

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Table 1 (*continued*)

Author, Year	Title	Journal	Study type	Participants	Eligibility criteria	Follow-up time	Examination methods	Main outcomes	mNOS rating	Evidence level
Crameri et al., 2020 [14]	Reduced maximal aerobic capacity after COVID-19 in young adult recruits, Switzerland, May 2020	Euro Surveillance	Prospective cohort study	199 (18-27y, 13% female)	RT-PCR confirmed	31–58 days (median 45d) post-diagnosis	Validated physical fitness test	19% of COVID- 19 convalescents with decrease of >10% in VO2 max	8	3
Frija-Masson et al., 2020 [15]	Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post-infection.	European Respiratory Journal	Retrospective cohort study	50 (46-62y, 44% female)	<85y old; respiratory symptoms; discharged from Bichat Hospital Paris; RT-PCR confirmed	30 days after symptom onset	Pulmonary functional status	27/50 with impaired lung function, mix of restrictive and low diffusion patterns	6	3
Zhao et al., 2020 [16]	Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery	EClinicalMedicine	Retrospective cohort study	55 (mean age 47y, SD 15.49, 41.82% female)	Diagnosis according to WHO interim guidance	3 months post-discharge	HRCT, lung function	Radiological abnormalities 70.91%; lung function abnormalities (e.g. diffusion reductions in DLCO) 25.45%; persistent gastrointestinal symptoms 31%, headache 18.18%, fatigue 16.36%, exertional dyspnea 14.55%	5	3
Wei et al., 2020 [17]	Analysis of thin-section CT in patients with coronavirus disease (COVID-19) after hospital discharge	Journal of X-Ray Science and Technology	Retrospective cohort study	59 (25-70y, 28/59 female)	RT-PCR confirmed	24–39 days post-admission	Thin-section thorax CT	Residual pulmonary fibrosis 39%	3	3
Yu et al., 2020 [18]	Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19	Korean Journal of Radiology	Retrospective cohort study	32 (30-65y, 10/32 female)	RT-PCR confirmed; been hospitalized and discharged; at least 2x thin-section CT during hospitalization	9 days post-discharge (20 days after disease onset)	Thin-section chest CT	14/32 with signs of pulmonary fibrosis	3	3
Patelli et al., 2020 [19]	Preliminary detection of lung hypoperfusion in discharged Covid-19 patients during recovery	European Journal of Radiology	Retrospective cohort study	20 (35-86y, 8/20 female)	Treated for SARS-CoV-2 pneumonia	14–60 days after remission of fever	Chest CT	8/20 with residual dyspnea associated with hypoperfused lung volume	5	3
You et al., 2020 [20]	Anormal pulmonary function and residual CT abnormalities in rehabilitating COVID-19 patients after discharge	Journal of Infection	Prospective cohort study	18 (28-67y, 8/18 female)	RT-PCR confirmed	40±11.6 (non-severe illness) and 34.7±16.5 (severe) days post-discharge	Pulmonary function test	5/12 non-severe and 2/5 severe patients with abnormal lung function; 83% with anormal CT (pulmonary fibrosis)	4	3
Hollingshead et al., 2020 [21]	Spontaneous Pneumothorax Following COVID-19 Pneumonia	IDCases	Case report	50y man	–	1 month after symptom onset	CT angiography	10 cm loculated pneumothorax; diffuse ground-glass opacities	–	5
Liu et al., 2020 [22]	The pulmonary sequelae in discharged patients with COVID-19: A short-term observational study	Respiratory Research	Retrospective cohort study	149 (36-56y, 55% female)	RT-PCR confirmed; discharged from hospital	1, 2 and 3 weeks post-discharge	Chest CT	Incomplete radiological resolution (residual fibrous stripes) 47% in 3rd week	3	3
Sahanic et al., 2020 [23]	Persisting pulmonary impairment following severe SARS-CoV-2 infection, preliminary results from the CovILD study	ERS International Congress	Prospective cohort study	82 (mean 57y, 36.6% female)	–	6 weeks post-discharge	Clinical examination, blood test, lung function, thoracic CT, echocardiography	66% with persistent symptoms (dyspnea, cough); 24% with persistent lung impairment; 59% with left ventricular diastolic dysfunction;	4	3
		Respiratory Research							4	3

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Table 1 (*continued*)

Author, Year	Title	Journal	Study type	Participants	Eligibility criteria	Follow-up time	Examination methods	Main outcomes	mNOS rating	Evidence level
Huang et al., 2020 [24]	Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase		Retrospective cohort study	57 (19-71y, 31/57 female)	>18y old; RT-PCR or next-generation sequencing confirmed	>30 days post-discharge	CT, lung function tests, 6 min walk test	Abnormal CT findings 54.3%; abnormal pulmonary function tests 75.4%; 4/57 with pulmonary fibrosis		
Cardiovascular & Haematological System										
Eiros et al., 2020 [25]	Pericarditis and myocarditis long after SARS-CoV-2 infection: a cross-sectional descriptive study in health-care workers	Preprint	Cross-sectional study	139 (IQR 41-57y, 72% female)	RT-PCR or serology confirmed	9.3–11.0 weeks after symptom onset	ECG, blood test, CMR	Diagnosis of pericarditis in 3%, myopericarditis in 11%, myocarditis in 26%; 42% with chest pain, dyspnea or palpitations; 50% with ECG abnormalities; 75% with CMR abnormalities; 73% with altered immune cell counts in blood	8	4[a]
Puntmann et al., 2020 [26]	Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered from Coronavirus Disease 2019 (COVID-19)	JAMA Cardiology	Prospective cohort study	100 (mean 49y, 47% female)	RT-PCR confirmed; resolution of respiratory symptoms; negative swab test at end of isolation period	64–92 days post-diagnosis	CMR, blood test	78% with abnormal CMR, 60% with ongoing myocardial inflammation	8	3
Rajpal et al., 2020 [27]	Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection	JAMA Cardiology	Prospective cohort study	26 (mean 19.5y, 42.3% female)	RT-PCR confirmed; athletes	11–53 days after recommended quarantine	CMR, ECG, blood test, echocardiogram	CMR findings consistent with myocarditis in 15%; CMR findings suggesting prior myocardial injury in 30.8%	3	3
Chen et al., 2020 [28]	Sudden severe thrombocytopenia in a patient in the recovery stage of COVID-19.	The Lancet Haematology	Case report	38y male	–	29 days after symptom onset	Blood test	Isolated thrombocytopenia (resolution through therapy in 2 weeks)	–	5
Neurological System & Mental Health										
Lu et al., 2020 [29]	Cerebral Micro-Structural Changes in COVID-19 Patients, An MRI-based 3-month Follow-up Study: A brief title: Cerebral Changes in COVID-19	EClinicalMedicine	Prospective cohort study	60 (mean 44.1y, 43.3% female)	RT-PCR confirmed; discharged from hospital in Fuyang	3 months	MRI, questionnaire	Possible disruption to micro-structural and functional brain integrity; 55% with persistent neurological symptoms (headache, memory loss, myalgia, mood change)	8	3
Morjaria et al., 2020 [30]	Bilateral lower limb weakness: a cerebrovascular consequence of covid-19 or a complication associated with it?	Internal and Emergency Medicine	Case report	49y male	–	1 month after symptom onset	Neurological examination	Persisting lower limb weakness	–	5
Taquet et al., 2020 [31]	Bidirectional associations between COVID-19 and psychiatric disorder: a study of 62,354 COVID-19 cases	Preprint	Retrospective cohort study	44′779 out of a cohort of 62′354 (mean 49.3y, 55.3% female)	Diagnosis of COVID-19 or pneumonia due to SARS-associated coronavirus, other coronavirus as cause of disease, coronavirus	14–90 days after diagnosis	Statistical analysis of cohort studies	Increased incidence of psychiatric diagnoses (anxiety, depression, insomnia, dementia) 5.8% vs. 2.5–3.4% in control	6	3[a]

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Table 1 (*continued*)

Author, Year	Title	Journal	Study type	Participants	Eligibility criteria	Follow-up time	Examination methods	Main outcomes	mNOS rating	Evidence level
					infection unspecified					
Mazza et al., 2020 [32]	Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors	Brain, Behavior, and Immunity	Prospective cohort study	402 (18-87y, 34.3% female)	COVID-19 survivors	31.29±15.7 days post-discharge or 28.56±11.73 days after ED evaluation	unstructured clinical interview, self-reported questionnaires	56% in clinical range of at least 1 psychopathological dimension (28% PTSD, 31% depression, 42% anxiety, 20% OC symptoms, 40% insomnia)	3	3
Otorhinolaryngological System										
Chary et al., 2020 [33]	Prevalence and Recovery From Olfactory and Gustatory Dysfunctions in Covid-19 Infection: A Prospective Multicenter Study.	American Journal of Rhinology & Allergy	Prospective cohort study	115 (20-83y, 70% female)	RT-PCR confirmed	15 days post-diagnosis	Telephone questionnaire	36% with incomplete olfactory (anosmia, hyposmia) or gustatory (ageusia, hypogeusia) recovery, 3% with lack of recovery	4	3
Kosugi et al., 2020 [34]	Incomplete and late recovery of sudden olfactory dysfunction in COVID-19.	Brazilian Journal of Otorhinolaryngology	Retrospective cohort study	145 (IQR 31-44y, 53.1% female) with positive COVID-19 test	–	12-39 (median 31) days after symptom onset	Online survey for physicians	No recovery in 13.9% and partial recovery in 33.6% with loss of olfaction	7	3
Lechien et al., 2020 [35]	Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study	European Archives of Oto-Rhino-Laryngology	Prospective cohort study	417 (19-77y, 263/417 female)	>18y old; RT-PCR confirmed	>15 days after onset of infection	Questionnaire	Anosmia recovery time > 15 days in 3.4%	4	3
Endocrinological System										
Ruggeri et al., 2020 [36]	Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic	Hormones	Case report	43y female	–	6 weeks after symptom onset	Physical examination, blood test	Subacute thyroiditis (resolution with therapy in 2 weeks)	–	5
Brancatella et al., 2020 [37]	Subacute Thyroiditis After Sars-COV-2 Infection.	The Journal of Clinical Endocrinology & Metabolism	Case report	18y female	–	15 days post-diagnosis	Physical examination, blood test	Subacute thyroiditis (resolution with therapy in 2 weeks)	–	5

[a] Preprints.

indirectly, there is the possibility of persistent damage with specific sequelae.

In this systematic review we provide an evaluation of data concerning COVID-19 intermediate and long-term sequelae published to date. This paper focuses on sequelae in previously healthy individuals. As COVID-19 is a relatively new disease entity the follow-up time in studies identified in our systematic search does not exceed 12 weeks. It is currently not possible to predict the longer-term impact of several months to years. It is conceivable that a lot of outcomes seen in the more short-term frame of two to six weeks are of transient nature. The WHO proposes a recovery time of up to two weeks for mild and up to six weeks for severe disease courses [40].

Our review, however, shows that a significant proportion of formerly healthy adults aged 18–50 years is affected by COVID-19 sequelae for longer periods. As they make up the majority of the working population, there will be longer term consequences and burdens not only for the health system but also for the economy.

4.1. General health

Regarding general health, there seems to be mounting evidence that a considerable number of COVID-19 convalescents will suffer from fatigue even weeks after the acute infection has subsided. Post-infectious fatigue months and even years after recovery has been previously observed in a variety of viral infections. There is evidence of chronic fatigue as a long-term consequence, especially in people younger than 30 years old, after epidemics of influenza A(H1N1) virus, SARS-CoV, Ebolavirus and West Nile virus. In some of these cases, the diagnostic criteria for Chronic Fatigue Syndrome were fulfilled. A miscommunication in the inflammatory response pathways, especially cytokine networks, might be the underlying cause [41]. It has been hypothesized that a COVID-19 infection might lead to a higher predisposition for a number of different cancer types. Hays et al. proposed an increased tumorigenesis through the activation of the MAPK and JAK-STAT pathway upon a COVID-19 infection and the weakened immune system following a cytokine storm [39].

4.2. Respiratory system

As seen in the results section, abnormalities in pulmonary function were observed in the lung function examination (e.g. as decrease in aerobic capacity or reduction in diffusion capacity) as well as radiologically. Even though a majority of patients recovered fully or were in the process of radiological and/or clinical resolution, it would not be surprising if lung damage in the form of residual pulmonary fibrosis persisted in the long-term. This would also be a plausible explanation as to why some patients experienced shortness of breath even at up to 12 weeks after hospital admission [10]. Again, there is evidence from the SARS and MERS pandemic that some patients experienced lung damage up to 15 years later [42].

4.3. Cardiovascular and hematological system

According to the studies found in this review, cardiac damage might be a significant long-term sequela. Myocarditis, perimyocarditis and pericarditis were diagnosed as late as 11 weeks after symptom of infection onset [25]. Rajpal et al. showed that cardiac consequences were also pronounced in younger athletes [27]. This is especially concerning as myocarditis can lead to sudden cardiac death. Even with apparently recovered cardiac function, there might still be a risk of coronary artery disease, atrial fibrillation or ventricular arrhythmias as a consequence of myocardial injury [43].

4.4. Neurological system and mental health

To date, there are few original data on neurological sequelae. Radiologically, there seem to be distinct changes in cerebral microstructure, especially in those areas related to memory and smell loss, compared to healthy controls [29]. However, there is widespread speculation concerning neurological long-term consequences [38,44–46]. Several authors speculate that SARS-CoV-2 might trigger neurodegenerative diseases like multiple sclerosis, Parkinson's disease and narcolepsy in predisposed individuals in the long-term [44–46]. The occurrence of anosmia and ageusia in some patients has even been associated with prodromal features of Parkinson's disease [44].

With over 44′000 study subjects, Taquet et al. performed the most extensive study in this review in terms of numbers [31]. They observed a significant increase in newly diagnosed psychiatric diseases like anxiety, depression, insomnia and dementia compared to an unaffected control group. Likewise, Mazza et al. found indications of at least one psychiatric disease (post-traumatic stress disorder, depression, anxiety, obsessive-compulsive disorder, insomnia) in 56% of study participants approximatively 30 days post-discharge. Extrapolated from experiences with SARS and MERS, where the prevalence of depression, anxiety and post-traumatic stress disorder was high even after 39 months, a considerable impact on mental health post COVID-19 should be anticipated [47].

4.5. Otorhinolaryngological system

All three included studies investigating olfactory and gustatory dysfunction found a lack of or incomplete recovery in a substantial part of participants. However, they have a rather short follow-up period of only two to five weeks. Imam et al. believe that COVID-19 related olfactory dysfunction follows a similar mechanism as the post-viral olfactory dysfunction seen with other viral infections such as influenza virus, rhinovirus, metapneumovirus or parainfluenza virus. So these sequelae may reduce over longer time periods [48].

4.6. Endocrinological and reproductive system

Concerning the endocrinological system, only two case reports were found of whom both described a case of subacute thyroiditis following a COVID-19 infection. As this constitutes only sparse evidence, a statement regarding the scope of long-term sequelae in this organ system cannot be made. Nevertheless, Mongioì et al. hypothesize a role of SARS-CoV-2 in pancreatic damage and subsequent development of diabetes, in hypothalamic-pituitary-adrenal axis dysfunction and adrenal insufficiency and in hypothalamic-pituitary-thyroid axis dysfunction with thyroid damage, as seen in SARS-CoV infection [49]. As ACE2 is highly expressed by the human testis, an infection might lead to testicular damage and associated male infertility [49,50].

4.7. Strengths and limitations

To our knowledge, this is the first systematic review on long-term sequelae of COVID-19. The strengths of our systematic review include the careful and thorough searches according to PRISMA guidelines and the thorough extraction and interpretation of selected papers. A further strength is the quality assessment of articles using the modified Newcastle-Ottawa Scale as well as the pyramid of evidence. A limitation of our work, common to all research on COVID-19 consequences, is the limited time frame to assess sequelae as the interval since the beginning of the COVID-19 pandemic and this systematic review is just seven months, allowing scant time for the evolution of longer-term implications. Due to the fact that there is a limited number of references as of yet, we did not investigate geographic differences in type of COVID-19 sequelae.

5. Conclusions

Even though our current knowledge suggests that most COVID-19 sequelae in young, previously healthy adults, are of transient nature, there are indications of multi-organ impact. The large global burden of cases worldwide suggests that we will most likely face an ongoing wave of COVID-19 sequelae. Close attention should be paid to residual impairments in multi-organ function, especially persistent reduced lung function and carditis, and to mental health and neurological sequelae including post-viral fatigue syndrome. We suggest that further research should include lung function tests and sensitive test batteries to detect long-lasting structural and functional damage to the cardiopulmonary and the neurological system. Patients suffering from post-viral fatigue syndrome and mental health impairments could be followed-up routinely with questionnaires to monitor disease course. In general, study test batteries to follow up on sequelae should be carefully designed to detect subtle, long-term sequelae.

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Declaration of competing interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2021.101995.

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